PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
KPZK/2005/PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/PL2005/000022	29.03.2005	29.03.2004

International Patent Classification (IPC) or national classification and IPC
INV. C07D235/30 A61K31/4184 A61P35/00

Applicant
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1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27.10.2005	04.08.2006

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/PL2005/000022

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-9, 12	as originally filed

Claims, Numbers

1-21	received on 27.10.2005 with letter of 03.10.2005

Drawings, Sheets

1/1	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1-21
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 20-21

because:

☒ the said international application, or the said claims Nos. 20-21 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	2-7,17,19,21
	No:	Claims	1,8-16,18,20
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

Basis of the report

1 With his letter of 03.10.2005 the applicant filed an amended set of claims. However, the application as originally filed does not provide a basis for the amended value "methyl" as R^1 and "C_{1-3}aliphatic group", "substituted at the position 2" and "dimethylamino group" concerning R^2 in amended claims 1 and 8. Furthermore, in the application as filed neither a basis can be found for the amended terms "C_{1-3}alkoxy", "C_{1-3}alkylsulfone", and "C_{1-3}alkylsulfoxide" in amended claim 9; nor for the amended terms "C_{1-3}aliphatic amine" and/or "dimethylamino group" in amended claims 10-12. None of these terms is disclosed in the original application documents. The amendments extend thus beyond the content of the application as originally filed, contrary to Articles 19(2) and 34(2)(b) PCT. In this context it is noted that generalisations of specific examples do not comply with the with the requirements of Articles 19(2) and 34(2)(b) PCT.

2 The present report has thus been established based on the original set of claims whereas the amended set of claims has not been considered for the purpose of the report (Rule 70(2)(c) PCT).

3 The application is directed to

(i) 2-NR^1R^2 substituted 4,5,6,7-tetrabromo-benzimidazoles (1) (claims 1-7),
(ii) a method for their preparation (claims 8-15),
(iii) a pharmaceutical composition with a compound (1) (claim 16),
(iv) a pharmaceutical composition with the specific compounds (1) of claims 2-7 (claim 17),
(v) the medical use of compounds (1) (claim 18),
(vi) the medical use of the specific compounds (1) of claims 2-7 (claim 19),
(vii) a therapeutic method involving compounds (1) (claim 20), and
(viii) a therapeutic method involving the specific compounds (1) of claims 2-7 (claim 21).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 20-21 relate to subject-matter considered by this Authority to be covered by the

provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents.

D1: PAGANO, M. A. *ET AL. J. MED. CHEM.*, vol. *47*, **2 December 2004**, pages 6239-6247.

D2: PAGANO, M. A. *ET AL. BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS*, vol. *321*, **3 September 2004**, pages 1040-1044.

D3: ANDRZEJEWSKA, M. *ET AL. BIOORG. MED. CHEM.*, vol. *11*, **2003**, pages 3997-4002.

D4: WO 03/030902 A, 17 April 2003.

D5: US-A-3 705 174, 5 December 1972.

D1 and **D2** were published after the priority date. Under the presumption that the priority is valid for the claimed matter these documents are not considered as prior art under Rule 64.1 PCT.

2 Novelty

2.1 **D3** discloses inter alia 2-Cl, 2-Br, 2-perfluoroalkyl, and 2-mercapto substituted 4,5,6,7-tetrabromo-benzimidazoles and their casein kinase 1 and 2 inhibitory activity. The present compounds (1) differ from the compounds of **D3** through their 2-NR^1R^2 substituent. The present claimed matter is thus novel vis-à-vis **D3**.

D4 relates to imidazole derivatives as modulators of interleukin-1 receptor-associated kinase. The compounds of **D4** (claim 19, formula IIa) generally comprise the present compounds (1), but the document does not specifically disclose them (cf. examples). Hence, the present claimed matter is considered as a novel selection of the compounds of **D1**, inter alia due to the four bromo substituents as novel technical features.

D5 shows to 2-polyhaloalkyl-benzimidazoles as anthelmetics and pesticides. The present compounds (1) differ from those of **D5** through the 2-NR^1R^2 substituent.

The present claimed matter is therefore novel in view of **D5**.

In view of **D3** to **D5** the application complies with the criterion of novelty.

2.2 **D1** and **D2** disclose the work of the present application and might become relevant to the question of novelty and inventive step if the present claimed date of priority could not be acknowledged.

3 Inventive Step

3.1 The application describes the synthesis of the specific compounds of claims 2-7 and shows that these compounds act as inhibitors of casein kinase 2 (the application, page 5, table 2).

3.2 **D3** describes already 2-substituted 4,5,6,7-tetrabromo-benzimidazoles as casein kinase 1 and 2 inhibitors. The present compounds (1) differ from those of **D3** in having a 2-NR^1R^2 substituent. In view of **D3** as most relevant state of the art, the problem underlying the application may be seen in the provision of further casein kinase inhibitors, particularly of casein kinase 2. **D3** teaches that the position 2 of benzimidazole casein kinase inhibitors is not apparently involved in the stabilization of the binding of the inhibitor in casein kinase 2. Based on the binding data of the 4,5,6,7-tetrabromo-benzimidazoles **1**, **2e**, **6**, **8a-d**, and **9** (with the following 2-substituents: **1**, hydrogen; **2e**, CF_3; **6**, Br; **8a**, C_2F_5; **8b**, C_3F_7; **8c**, C_4F_9; **8d**, Cl; **9**, SH) the authors of **D3** draw the conclusion that the main contacts between this type of inhibitors and the nucleotide cavity of casein kinase 2 are occurring only at the benzene side of the benzimidazole molecule while the imidazole moiety appears rather unimportant (cf. page 4000, paragraph 1). In the light of that teaching of **D3**, it appears that the skilled person has had reasonable expectation of success that also the present compounds (1) would exhibit the desired casein kinase 2 inhibitory activity, at least to a certain extend. Merely as a solution of providing further casein kinase 2 inhibitors, the present compounds (1) would therefore be considered as obvious alternatives of the compounds of **D3**.

Despite this, the comparison of the protein kinase 2 binding data provided in **D3** (table 1) and in the present application for the compounds of claims 2-7 (page 5, table 2) with 4,5,6,7-tetrabromobenzimidazole as reference compound in both sets of test results (**D3**: K_i = 0.50 µM; present application: K_i = 0.30 µM) shows that the specific 2-NR^1R^2 substituted compounds (1) of the present claims 2-7 are more potent casein kinase 2 inhibitors (K_i values of 0.04-0.16 µM) than the corres-

ponding 2-substituted 4,5,6,7-tetrabromo-benzimidazoles of **D3** (K_i values of 0.40-1.48 µM). Since this improved potency is not obvious in view of the cited prior art, the subject-matter of the present claims 2-7, 17, 19, and 21 appears to involve an inventive step.

However, no inventive step would be acknowledged for the whole scope of the present claims 1, 8-16, 18, and 20 for the following reasons. A technical effect (in the present case the improved casein kinase 2 inhibitory effect of the compounds of claims 2-7) which justifies the selection of the claimed compounds must be one which can be fairly assumed to be produced by substantially all the compounds claimed. The terms "aliphatic group", "optionally substituted with a substituent", and "substituted amino group" used in the present claims 1, 8, 9, 18, and 20 are open-ended and thus likely to comprise structures which neither exhibit the desired casein kinase inhibitory activity, let alone an improved potency over the compounds of **D3**. For that reason no inventive step would be acknowledged for open-ended compounds (1) according to claim 1 and subject-matter referring to such compounds according to the claims 8-16, 18, and 20.

Consequently, the claims 1, 8-16, 18, and 20 do not meet the requirements of inventive step.

4 Industrial Applicability

For the assessment of the present claims 20-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII
Certain defects in the international application

1 The relevant background art disclosed in **D3** is not mentioned in the description, nor is this document identified therein (Rule 5.1(a)(ii) PCT).

2 The references "Pease and Gardiner, 1969" (page 1, line 9) and "Sarno et al., 2001" (page 2, line 2) are incomplete and may read "Pease and Gardiner *J. Agric.*

Food Chem. **1969**, *17*, 268-270" and "Sarno *et al. FEBS Lett.* **2001**, *496*, 44-48". Furthermore, the reference to Andrzejewska *et al.* on page 1, lines 19-20 reads correctly "Andrzejewska *et al. Eur. J. Med. Chem. 37* (**2002**), 973-978" (note that the page no. 972 is incorrect in the given citation).

Re Item VIII

Certain observations on the international application

The application does not comply with the requirements of Article 6 PCT for the following reasons.

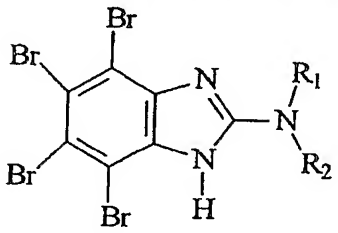
1 The expression "such as" used in claims 1 and 9 has no limiting effect on the scope of these claims. The technical features following this expression are thus superfluous, thereby resulting in a lack of conciseness of the claims.

2 The term "lower aliphatic amine" used in claims 10 and 12 lacks clarity with regard to the maximum number of carbon atom which distinguishes "lower" from non-lower aliphatic amines.

3 In Claims 20 and 21 the therapeutic application is functionally defined by a mechanism of action which does not allow any practical application in the form of a defined, real treatment of a pathological condition. The objection could be overcome by either introducing in the claims a list of pathological conditions cited in the application, or by showing that means are available which would allow the skilled person to recognise which additional conditions would fall within the functional definition.

Claims

1. New derivatives of 4,5,6,7-tetrabromobenzimidazole of formula 1



Formula 1

wherein R_1 is hydrogen or methyl group, R_2 is (C_1-C_3)aliphatic group or (C_1-C_3)aliphatic group substituted at the position 2 with hydroxyl or dimethylamino group.

2. A new derivative according to Claim 1, which is 2-methylamino-4,5,6,7-tetrabromo-1H-benzimidazole.

3. A new derivative according to Claim 1, which is 2-dimethylamino-4,5,6,7-tetrabromo-1H-benzimidazole.

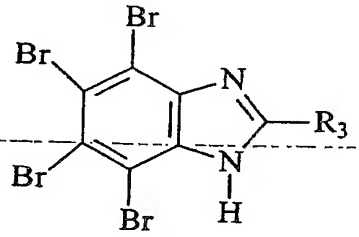
4. A new derivative according to Claim 1, which is 2-ethanolamino-4,5,6,7-tetrabromo-1H-benzimidazole.

5. A new derivative according to Claim 1, which is 2-isopropylamino-4,5,6,7-tetrabromo-1H-benzimidazole.

6. A new derivative according to Claim 1, which is 2-(2-hydroxypropylamino)-4,5,6,7-tetrabromo -1H-benzimidazole.

7. A new derivative according to Claim 1, which is 2-(2-dimethylaminoethylamino)-4,5,6,7-tetrabromo -1H-benzimidazole.

8. A method of preparation of new derivatives of 4,5,6,7-tetrabromobenzimidazole of formula 1, wherein R_1 is hydrogen or methyl group, R_2 is (C_1-C_3)aliphatic group or (C_1-C_3)aliphatic group substituted at the position 2 with hydroxyl or dimethylamino group in the reaction of the compound of formula 2,



Formula 2

wherein the substituent R_3 is halogen, alkylthio group or lower alkoxy group or other group easily being substituted, with an amine, at elevated temperature, and then the resulting product is purified by crystallization or chromatography on silica gel.

9. The method according to Claim 8 wherein in the compound of formula 2, the substituent R_3 is halogen consisting of Cl or Br, or alkylthio group consisting of CH_3S, C_2H_5S, C_3H_7S, or (C_1-C_3)alkoxy group consisting of CH_3O, C_2H_5O or other group easily being substituted consisting of (C_1-C_3)alkylsulfone group or (C_1-C_3)alkylsulfoxide group.
10. The method according to Claim 8 wherein as the amine, a primary (C_1-C_3)aliphatic amine is used.
11. The method according to Claim 10 wherein the primary (C_1-C_3)aliphatic amine includes in the aliphatic chain additionally hydroxyl groups or dimethylamino group.
12. The method according to Claim 8 wherein as the amine, a secondary (C_1-C_3)aliphatic amine is used.
13. The method according to Claim 8 wherein the amine is used both as a reagent and a solvent in an aqueous or alcoholic solution.
14. The method according to Claim 8 wherein the reaction of the compound of formula 2 with the amine is carried out within the temperature range from 80 to 140 °C.
15. The method according to Claim 8 wherein the compounds of formula 1 can be converted by a known method into salts of mineral or organic acids.
16. A pharmaceutical composition exhibiting anti-neoplastic activity, containing effective anti-neoplastic acting amount of the compound according to Claim 1, combined with at least one inert, pharmaceutically acceptable carrier or diluent.
17. A pharmaceutical composition exhibiting anti-neoplastic activity, containing effective, anti-neoplastic acting amount of the compound according to any one of Claims 2 - 7, combined with at least one inert, pharmaceutically acceptable carrier or diluent.
18. Use of new derivatives according to Claim 1 for manufacturing of a drug having anti-neoplastic activity.
19. Use of new derivatives according to any of the Claims 2 - 7 for manufacturing of a drug having anti-neoplastic activity.
20. A method of inhibiting caseine kinase activity 2 in patients in need of such treatment by administration of effective amount of the compound of formula 1 according to Claim 1.
21. A method of inhibiting caseine kinase activity 2 in patients in need of such treatment by administration of effective amount of the compound of formula 1 according to any of the Claims 2-7.